

Metformin: A First-Line Pharmacotherapy in Type-2 Diabetes Mellitus

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Abstract

Type 2 diabetes mellitus (T2DM) represents a major global health challenge, affecting over 500 million adults worldwide and contributing significantly to cardiovascular morbidity and mortality. Metformin has remained the cornerstone of T2DM management for decades, maintaining its position as the recommended first-line therapy in international treatment guidelines. This review comprehensively examines metformin's evolving role from its historical origins to contemporary applications and future directions. Initially derived from *Galega officinalis* (French lilac), metformin's mechanism primarily involves AMP-activated protein kinase (AMPK) activation and hepatic gluconeogenesis suppression, though emerging research continues to reveal additional molecular targets. The drug's enduring preference stems from its favorable efficacy-safety profile, cost-effectiveness, weight-neutral properties, and proven cardiovascular benefits demonstrated in landmark studies like the UK Prospective Diabetes Study (UKPDS). Recent years have witnessed expanded applications, including revised safety guidelines for renal impairment, investigations into potential anti-cancer effects, and exploration of its role in healthy aging. While newer antihyperglycemic agents with demonstrated cardiorenal benefits have emerged, metformin maintains fundamental importance in treatment algorithms, either as monotherapy or in combination regimens. Future perspectives include optimizing personalized therapy approaches, exploring novel formulations, and investigating metformin's potential in metabolic disease prevention. This review synthesizes current evidence supporting metformin's ongoing relevance while addressing contemporary challenges in its positioning within an increasingly complex therapeutic landscape for T2DM management.

Keywords: Type 2 diabetes, Metformin, First-line therapy, AMPK, Cardiovascular protection, Drug safety.

1. Introduction

1.1 The Global Burden of Diabetes and the Ascendancy of Type 2 Diabetes Mellitus

Diabetes mellitus represents one of the most significant public health challenges of the 21st century, posing a substantial threat to global health systems and economies. According to the International Diabetes Federation, the global prevalence of diabetes has reached pandemic proportions, affecting over half a billion adults worldwide. This number is projected to rise precipitously, underscoring a relentless and expanding epidemic. The societal and economic burdens are staggering, encompassing direct medical costs and the profound indirect costs

associated with disability, lost productivity, and premature mortality.[1] The overwhelming majority of this burden, approximately 90-95% of all cases, is attributable to Type

1.2 Diabetes Mellitus (T2DM). Once considered a disease of affluent, aging populations

T2DM now exhibits a rapidly shifting epidemiology, with a dramatic increase in incidence in low- and middle-income countries and a disturbing trend towards diagnosis in younger adults, adolescents, and even children. This shift is inextricably linked to global transitions towards urbanized lifestyles

characterized by sedentary behavior, dietary patterns high in processed foods and sugars, and the consequent rise in obesity. The escalating prevalence of T2DM is not merely a statistical concern but a clarion call for enhanced prevention strategies and the optimization of effective, accessible, and sustainable long-term management protocols.[2]

1.3 Pathophysiology of T2DM: A Dual Defect of Insulin Resistance and β -Cell Dysfunction

The development and progression of T2DM are underpinned by a complex pathophysiology, primarily characterized by two core defects: insulin resistance and the progressive failure of pancreatic β -cell function. These two processes engage in a detrimental interplay that defines the natural history of the disease.[3]

1.4 The Multifarious Complications of Uncontrolled Diabetes

The primary clinical significance of uncontrolled hyperglycemia lies in the development of debilitating and life-threatening microvascular and macrovascular complications. These complications are a major source of morbidity, reduced quality of life, and mortality for individuals with T2DM.[4]

1.5 The Central Role of Oral Antidiabetic Therapy in Disease Management

The management of T2DM is multifaceted, involving lifestyle modifications (medical nutrition therapy and physical activity) as the essential foundation. However, for the vast majority of patients, pharmacological intervention is necessary to achieve and sustain glycemic targets. Within the pharmacological armamentarium, oral antidiabetic agents (OADs) play a pivotal and often initial role.[5]

2. History of Metformin (Past)

2.1 Botanical Origins: The Legacy of Galega officinalis

The story of metformin begins not in a modern laboratory, but in the fields and apothecaries of

medieval Europe. For centuries, the perennial herb *Galega officinalis*, commonly known as French lilac or goat's rue, was employed in traditional folk medicine to alleviate the symptoms of a condition then recognized as "sweet urine." Historical records, including Culpeper's *Complete Herbal* from 1653, document its use for polyuria and other ailments, as well as its application as a galactagogue to enhance milk production in livestock.[6] The plant's efficacy was later attributed to its high concentration of guanidine, a compound with known glucose-lowering properties. However, the natural guanidine derivative in the plant, galegine, was too toxic for safe, long-term human use. This botanical foundation provided the crucial chemical clue that would eventually lead to the development of synthetic biguanides, demonstrating a classic example of pharmacognosy—where natural remedies inspire modern pharmaceuticals.[7]

The 19th century marked the transition from botanical extract to chemical synthesis. In 1844, German chemist Adolph Strecker first described the synthesis of guanidine. Decades later, in 1878, Bernhard Rathke developed the synthesis of biguanides, creating the core chemical structure that would define the drug class. The therapeutic potential of these compounds was first observed in 1918 when guanidine hydrochloride was shown to lower blood glucose in rabbits. However, the pivotal moment came in 1922 when Werner and Bell successfully synthesized dimethylbiguanide—the compound we now know as metformin. Despite this early breakthrough, the discovery of insulin in the same year shifted scientific attention away from oral antidiabetic agents, delaying metformin's clinical development for several decades.[8]

2.2 The Rise and Fall of Early Biguanides: Phenformin and Buformin

The mid-20th century witnessed the first clinical application of biguanides, though not initially metformin. The 1920s saw the introduction of Synthalin A and B (decamethylene diguanide and dodecamethylene diguanide, respectively), but these were withdrawn by the 1940s due to significant hepatotoxicity and nephrotoxicity. In the 1950s, two more potent biguanides emerged:

phenformin (phenethylbiguanide) and buformin (butylbiguanide). These agents were widely adopted in Europe and the United States due to their potent hypoglycemic effects.[9]

However, by the 1970s, a troubling association between phenformin and an elevated risk of lactic acidosis a serious and often fatal metabolic condition—became undeniable. The risk was particularly high in patients with renal impairment or other conditions predisposing to hypoxemia. This led to the withdrawal of phenformin from most markets, including a formal FDA-mandated withdrawal in the United States in 1978. Buformin met a similar fate. The downfall of these early biguanides cast a long shadow over the entire drug class, instilling a deep-seated caution regarding their use and significantly hindering the acceptance of metformin for years.

3. Mechanism of Action: A Multi-Targeted Approach to Metabolic Health

The pharmacological agent in question represents a cornerstone in the management of type 2

diabetes mellitus (T2DM) and related metabolic disorders. Its efficacy stems not from a single, isolated action, but from a complex and synergistic interplay of mechanisms across multiple organ systems. The primary effects include the inhibition of hepatic glucose production, enhancement of peripheral glucose utilization, modulation of gut microbiota, and beneficial impacts on weight and

lipid metabolism. The central player mediating many of these effects is the activation of the AMP-activated protein kinase (AMPK) pathway, a master regulator of cellular energy homeostasis.[10]

3.1 Primary Action: Inhibition of Hepatic Gluconeogenesis

The most well-established and potent effect of this drug is the reduction of fasting blood glucose levels through the suppression of excessive glucose production in the liver (hepatic gluconeogenesis).[11]

AMPK-Dependent Mechanism: The drug's entry into hepatocytes (liver cells) leads to a mild and specific inhibition of the mitochondrial respiratory chain complex I. This inhibition is not severe enough

to cause cellular damage but does cause a transient reduction in ATP production and a concomitant increase in the cellular AMP-to-ATP ratio. This energy stress is the primary trigger for the activation of AMPK.[12]

Downstream Effects of AMPK Activation: Once activated, AMPK orchestrates a program of energy conservation and glucose suppression. Key actions include:

Inhibition of Key Gluconeogenic Enzymes: AMPK phosphorylates and inhibits critical transcriptional coactivators like PGC-1 α (Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha) and TORC2 (Transducer of Regulated CREB activity 2). This leads to the downregulation of the gene expression for gluconeogenic enzymes such as Phosphoenolpyruvate

carboxykinase (PEPCK) and Glucose-6-phosphatase (G6Pase), effectively shutting down the liver's machinery for making new glucose.[13]

Promotion of Catabolic Pathways: Simultaneously, AMPK promotes energy-producing pathways like fatty acid oxidation.

AMPK-Independent Mechanisms: Recent research suggests that the drug's effect on the liver is not exclusively dependent on AMPK. An alternative pathway involves the reduction of hepatic energy charge (increased AMP/ADP) leading to the inhibition of the enzyme adenylate cyclase. This reduces levels of cyclic AMP (cAMP), which in turn dampens Protein Kinase A (PKA) activity. Since PKA is a positive regulator of gluconeogenesis, its inhibition further contributes to reduced glucose output.

4. Pharmacokinetics and Formulations of Metformin

4.1 Introduction to Pharmacokinetic Properties

Metformin hydrochloride exhibits distinctive pharmacokinetic characteristics that have significant implications for its clinical use in managing type 2 diabetes mellitus. Understanding these properties is essential for optimizing therapeutic outcomes while minimizing adverse effects. The drug's pharmacokinetic profile is characterized by incomplete but adequate oral absorption, minimal protein binding, absence of hepatic metabolism,

and predominantly renal elimination. These features collectively contribute to metformin's well-established safety profile and influence the development of various pharmaceutical formulations designed to enhance patient tolerance and adherence.[14]

4.2 Absorption Characteristics and Bioavailability

The journey of metformin begins with oral administration, where it undergoes absorption primarily in the small intestine. The drug demonstrates an absolute oral bioavailability of approximately 50-60%, which is considered moderate and sufficient for therapeutic efficacy. This limited bioavailability stems from metformin's high hydrophilicity and its dependence on active transport mechanisms across the intestinal epithelium. The absorption process follows saturable kinetics, meaning that increasing the dose beyond a certain point does not result in proportional increases in plasma concentration. This unique property contributes to metformin's wide therapeutic window and reduced risk of dose-related toxicity. Food intake affects the rate but not the extent of absorption, with concomitant food administration slowing absorption and potentially improving gastrointestinal tolerance.[15]

4.3 Distribution Patterns and Protein Binding

Following absorption, metformin distributes widely throughout the body tissues. The drug's volume of distribution typically ranges between 63 and 276 liters, indicating extensive tissue penetration. Unlike many pharmaceutical agents, metformin demonstrates negligible binding to plasma proteins, with studies showing less than 5% protein binding. This characteristic ensures that nearly the entire circulating drug fraction remains pharmacologically active and available for tissue uptake. The drug shows particular affinity for tissues such as the liver, kidneys, and intestinal mucosa, with concentrations in these organs often exceeding plasma levels. This tissue distribution pattern is clinically relevant given that the liver serves as metformin's primary site of action for its glucose-lowering

effects.[16]

4.4 Metabolism and Elimination Pathways

A distinctive feature of metformin's pharmacokinetics is its minimal metabolism within the human body. The drug undergoes no significant hepatic transformation via cytochrome P450 enzymes or other metabolic pathways, remaining largely unchanged throughout its residence in the body. This absence of metabolism significantly reduces metformin's potential for pharmacokinetic drug interactions involving metabolic enzymes. Elimination occurs predominantly through renal excretion, with the kidneys responsible for clearing approximately 90% of the administered dose. Renal elimination involves both glomerular filtration and active tubular secretion. The mean elimination half-life ranges from 4 to 8.7 hours, with an average of approximately 6 hours in individuals with normal renal function. This relatively short half-life necessitates multiple daily dosing for immediate-release formulations to maintain therapeutic concentrations.[17]

4.5 Clinical Considerations and Therapeutic Implications

The pharmacokinetic properties of metformin directly inform important clinical considerations. The dependence on renal elimination necessitates dosage adjustment in patients with impaired kidney function, with current guidelines recommending assessment of renal function before initiation and periodically during treatment. The development of extended-release formulations has particularly benefited patients who experience gastrointestinal side effects with immediate-release metformin, thereby reducing treatment discontinuation rates. Understanding the pharmacokinetic profile enables healthcare providers to make informed decisions regarding dosing schedules, formulation selection, and individualization of therapy to maximize therapeutic benefits while minimizing adverse effects in the management of type 2 diabetes mellitus.[18]

5. Clinical Applications of Metformin: Present Therapeutic Role and Emerging Potential

5.1 Primary Application: Cornerstone Therapy in Type 2 Diabetes Mellitus

5.1.1 Monotherapy in Treatment-Naïve Patients

Metformin remains the foundational pharmacological intervention for Type 2 Diabetes Mellitus (T2DM), endorsed as first-line therapy by major international guidelines including the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD). Its initiation typically follows the diagnosis of T2DM when lifestyle modifications alone prove insufficient to achieve glycemic targets. The drug demonstrates robust efficacy, reducing HbA1c by approximately 1.0-2.0% while offering several distinct advantages over other antidiabetic agents. As monotherapy, metformin provides effective glycemic control without significant risk of hypoglycemia, weight gain, or fluid retention—common limitations associated with other glucose-lowering medications. The United Kingdom Prospective Diabetes Study (UKPDS) established metformin's long-term benefits, demonstrating not only sustained glycemic control but also significant reductions in diabetes-related endpoints and myocardial infarction in overweight patients.[19]

5.1.2 Combination Therapy in Advanced Disease

As T2DM progresses, characterized by declining β -cell function, metformin serves as the optimal base therapy for combination regimens. Its complementary mechanisms of action allow for synergistic effects when combined with other antidiabetic classes: With SGLT2 Inhibitors: Addresses multiple pathophysiological defects hepatic glucose production (metformin) and renal glucose reabsorption (SGLT2 inhibitors) With GLP-1 Receptor Agonists: Provides complementary insulin-sensitizing effects while benefiting from GLP-1 RA-mediated insulin secretion and appetite suppression With DPP-4 Inhibitors: Enhances insulin sensitivity while prolonging incretin action With Insulin: Reduces insulin requirements and mitigates weight gain associated with insulin therapy The flexibility of

metformin in combination regimens, available in fixed-dose combinations with most other antidiabetic classes, simplifies treatment intensification while maintaining its metabolic benefits throughout the disease continuum.

6. Secondary Applications: Expanding Therapeutic Horizons

6.1 Polycystic Ovary Syndrome (PCOS)

Metformin has established an important role in managing PCOS, particularly in women with insulin resistance. Its benefits extend beyond glycemic control to address fundamental metabolic disturbances in PCOS: Improvement in insulin sensitivity and reduction of hyperinsulinemia Restoration of ovulatory cycles and improvement in fertility outcomes Reduction in circulating androgen levels, ameliorating hirsutism and can Potential improvement in endometrial receptivity Positive effects on metabolic parameters including lipid profiles While not FDA-approved for this indication, metformin represents an important off-label option, especially for PCOS patients with impaired glucose tolerance or those seeking conception.

6.2 Obesity and Metabolic Syndrome

In individuals with obesity an metabolic syndrome, metformin offers several advantageous effect: Modest weight reduction or weight stabilization (approximately 2-3 kg over 1-2 yea Improvement in insulin sensitivity independent of weight loss Favorable effects on lipid metabolism—reducing triglycerides and LDL cholesterol Reduction in inflammatory marker associated with cardiovascular risk Potential prevention of diabetes progression in high-risk individuals Though the magnitude of weight loss is less pronounced than with newer anti-obesity medications, metformin's safety profile and metabolic benefits make it a valuable option, particularly in prediabetic obese individuals.

7. Cardiovascular Benefits: Beyond Glycemic Control

7.1 Legacy of Cardioprotection: UKPDS Insights

The UKPDS (1998) provided landmark evidence for metformin's cardiovascular benefits, demonstrating a significant 39% reduction in myocardial infarction and 36% reduction in all-cause mortality in overweight T2DM patients treated with metformin compared to conventional therapy. These benefits were substantially greater than those observed with insulin or sulfonylureas, despite similar glycemic control, suggesting pleiotropic cardioprotective mechanisms beyond glucose-lowering.

7.2 Contemporary Context: Comparison with Newer Agents

While newer classes like SGLT2 inhibitors and GLP-1 receptor agonists have demonstrated robust cardiovascular outcome benefits in recent trials (EMPA-REG, LEADER, etc.), metformin maintains relevance through:

- Cost-effectiveness: Remains the most economical option for cardiovascular risk reduction
- Complementary mechanisms: Can be combined with newer agents for additive benefits
- Long-term safety data: Decades of clinical experience support its cardiovascular safety
- Foundation therapy: Continues to serve as the base upon which cardioprotective regimens are built

Current guidelines position metformin as the initial therapy, with early addition of SGLT2 inhibitors or GLP-1 RAs in patients with established cardiovascular disease or high cardiovascular risk.

8. Emerging Applications: Frontiers of Metformin Research

8.1 Anti-Aging and Longevity

Preclinical and epidemiological evidence suggests metformin may influence aging processes through multiple pathways:

- AMPK activation: Mimics aspects of caloric restriction, a known longevity intervention
- Reduction of chronic inflammation: Addresses inflamm-aging, a hallmark of aging
- Improvement in cellular metabolism: Enhances mitochondrial function and reduces oxidative
- Potential effects on telomere maintenance: May slow cellular aging processes

The TAME (Targeting Aging with Metformin)

trial aims to investigate whether metformin can delay the development or progression of age-related chronic diseases in non-diabetic older adults. If successful, this could represent a paradigm shift in preventive medicine.

8.2 Cancer Prevention and Adjunct Therapy

Epidemiological studies consistently demonstrate reduced cancer incidence and improved cancer outcomes in diabetic patients using metformin. Proposed mechanisms include:

- Systemic effects: Reduction in insulin and IGF-1 levels, mitogens for many cancers
- Direct cellular effects: Inhibition of mTOR signaling and cancer cell proliferation
- Metabolic effects: Induction of energetic stress in cancer cells with high metabolic demand
- Immunological effects: Potential enhancement of anti-tumor immune responses

Ongoing clinical trials are investigating metformin as an adjunct to conventional cancer therapies in various malignancies, including breast, prostate, and colorectal cancers.

8.3 Neuroprotection and Cognitive Health

Emerging evidence suggests potential benefits in neurological disorders:

- Alzheimer's disease: Improved cognitive outcomes in diabetic patients
- Parkinson's disease: Potential neuroprotective effects through AMPK-mediated pathways
- Stroke recovery: Enhanced neurological recovery in experimental models

While clinical evidence remains preliminary, metformin's effects on cerebral metabolism, neuroinflammation, and vascular health warrant further investigation in neurological disorders.

9. Future Directions and Clinical Implications

The therapeutic landscape for metformin continues to evolve, with several important considerations:

- Personalized medicine approaches: Genetic factors influencing metformin response
- Novel formulations: Enhanced delivery systems for improved tissue targeting
- Combination strategies: Optimal sequencing with newer antidiabetic classes

Adverse Effects and Clinical Limitations of **Metformin**

I. Safety Profile

Metformin maintains an overall favorable safety reputation supported by decades of clinical use, yet certain adverse effects and contraindications require careful consideration in therapeutic decision-making. While generally well-tolerated, understanding its side effect profile enables optimal patient management and risk mitigation strategies across diverse clinical scenarios.[20]

II. Gastrointestinal Intolerance

The most prevalent adverse effects involve the gastrointestinal system, affecting a substantial minority of patients particularly during treatment initiation. These symptoms typically include transient nausea, abdominal discomfort, diarrhea, and occasional metallic taste perception. The underlying mechanisms involve complex interactions with intestinal serotonin release, gut microbiota modifications, and bile acid metabolism alterations.[21]

Clinical management strategies employ several effective approaches: Initiation with low doses (500 mg daily) followed by gradual upward titration Consistent administration with meals to moderate absorption kinetics Consideration of extended-release formulations demonstrating superior tolerability profiles Patient education regarding the typically self-limiting nature of these symptoms. [22]

III. Metabolic Considerations

A. Lactic Acidosis Risk

This rare but serious complication has historically influenced prescribing patterns, though contemporary understanding suggests exaggerated concerns with appropriate patient selection. Predisposing factors include: Significant renal impairment (eGFR <30 mL/min/1.73m²) Hemodynamic instability or hypoperfusion states Acute medical illnesses predisposing to metabolic acidosis Concurrent medications with similar metabolic effects Preventive protocols emphasize: Regular renal function assessment before and during therapy Temporary discontinuation during acute intercurrent illnesses. Avoidance in clinical scenarios predisposing to tissue hypoperfusion.

[23]

10. Conclusion:

The Enduring Legacy and Future Promise of Metformin Metformin stands as a remarkable testament to the evolution of pharmacotherapy in type 2 diabetes mellitus. From its botanical origins in French lilac to its current status as the foundational therapy in diabetes management, this biguanide derivative has consistently demonstrated unparalleled clinical value. Its position as the cornerstone of T2DM treatment remains firmly established, supported by decades of clinical experience and robust evidence from landmark trials. The drug's unique combination of efficacy, safety, affordability, and metabolic benefits continues to make it the preferred initial pharmacological intervention in clinical practice guidelines worldwide. The understanding of metformin's mechanisms and benefits has expanded significantly beyond its glucose-lowering properties. Its pleiotropic effects encompassing improvements in lipid metabolism, anti-inflammatory actions, cardiovascular protection, and potential oncological benefits reveal a multifaceted agent that addresses several pathophysiological aspects of metabolic disease. The demonstrated cardiovascular risk reduction in overweight diabetic patients, as established by the UKPDS, represents a particularly significant advantage that has endured the test of time. Furthermore, the recent relaxation of restrictions regarding its use in patients with mild to moderate renal impairment reflects an evolving appreciation of its safety profile when appropriately monitored. The future of metformin appears increasingly promising as research continues to uncover potential applications beyond its traditional metabolic indications. Ongoing investigations into its anti-aging properties, neuroprotective effects, and cancer preventive potential suggest that this ancient remedy may find new relevance in modern therapeutic areas. The TAME trial and similar initiatives represent pioneering efforts to explore metformin's potential in modifying fundamental biological processes rather than simply treating individual diseases.

However, the evolving landscape of diabetes therapeutics, with the emergence of newer agents demonstrating robust cardiorenal benefits, necessitates a nuanced approach to metformin's positioning. While its foundational role remains secure, future treatment algorithms may increasingly emphasize personalized approaches that incorporate patient-specific factors such as cardiovascular risk, renal function, and individual treatment goals. The absence of direct comparative outcome trials with newer agents highlights an important evidence gap that future research should address. In conclusion, metformin's journey from traditional medicine to modern therapeutics exemplifies the successful translation of pharmacological insights into clinical practice. Its enduring relevance stems from a favorable balance of efficacy, safety, and cost-effectiveness that few other medications can match. As research continues to elucidate its full therapeutic potential, metformin will likely maintain its central role in diabetes management while potentially expanding into novel clinical domains. The ongoing exploration of this remarkable drug serves as a powerful reminder that sometimes the most valuable therapeutic agents are those that continue to reveal new dimensions of clinical utility long after their initial discovery.

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